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ORIGINAL ARTICLE

In vitro Evaluation of Dry Powder Inhaler Devices of Corticosteroid Preparations

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ABSTRACT

Background: Although investigations of the drug aerosols generated from inhaled corticosteroid (ICS) preparations and combined drug preparations provide basic information about inhalation therapy, many clinicians have one-sided data about the precision of drug aerosols from the manufacturer. The present study was conducted to analyze and compare the performances of dry powder inhaler (DPI) devices of ICS and combined drug preparations.

Methods: The particle size of individual aerosols was measured according to the time-of-flight principle in terms of their aerodynamic diameter by using the aerodynamic particle sizer spectrometer Model 3321. Percent aerosolization was measured using only stage #0 and backup filters of the Andersen non-viable sampler model AN-200.

Results: The particle size distribution of aerosols generated from a Turbuhaler™ and Twisthaler™ showed a mono-modal distribution of less than 5 μm. In contrast, Diskus™ showed a polydisperse distribution, ranging from 0.5 to 20 μm. The percentages of DPI preparations converted into aerosols with a particle size less than 11 μm at a suction flow rate of 28.3 L/min were 5.7-6.2% for Diskus, 37.5-47.0% for Turbuhaler, and 19.8% for Twisthaler. At a suction flow rate of 60 L/min, the conversion percentages for DPI preparations into aerosols with a particle size less than 7.6 μm were 5.9-7.5%, 78.2-86.7%, and 43.5%, respectively.

Conclusions: Because *in vitro* differences in the aerosolization among different DPI devices containing ICS and combined drug preparations were observed, prescribers of these preparations should consider whether the patients will benefit more from the treatment of the central airways versus the peripheral airways.

KEY WORDS

aerosolization, devices, dry powder inhaler (DPI), inhaled corticosteroid (ICS), particle size

ABBREVIATIONS

APS, aerodynamic particle sizer; BFC, combination of BUD and formoterol; BUD, budesonide; DPI, dry powder inhaler; FP, fluticasone; ICS, Inhaled corticosteroid; MF, mometasone furoate; MMAD, mass median aerodynamic diameter; SFC, combination of FP and salmeterol xinafoate.

INTRODUCTION

Inhaled corticosteroid (ICS) and a combination of ICS and a long-acting β_2 stimulant (LABA) are used as first-line drugs for the long-term management of asthmatic patients. At present in Japan, the ICS preparations available for application with a dry powder inhaler (DPI) are fluticasone propionate (FP)-DPI, budesonide (BUD)-DPI, and mometasone furoate (MF)-DPI. In addition to these preparations, the combination of FP and salmeterol xinafoate (SFC)-DPI and that of BUD and formoterol (BFC)-DPI are available. Although the anti-asthmatic effects of these preparations have been evaluated in premarketing clinical trials, detailed data on the performances of devices for DPI preparations are limited.

We have previously reported in Japan[1] the precise distribution of the particle size of aerosols generated

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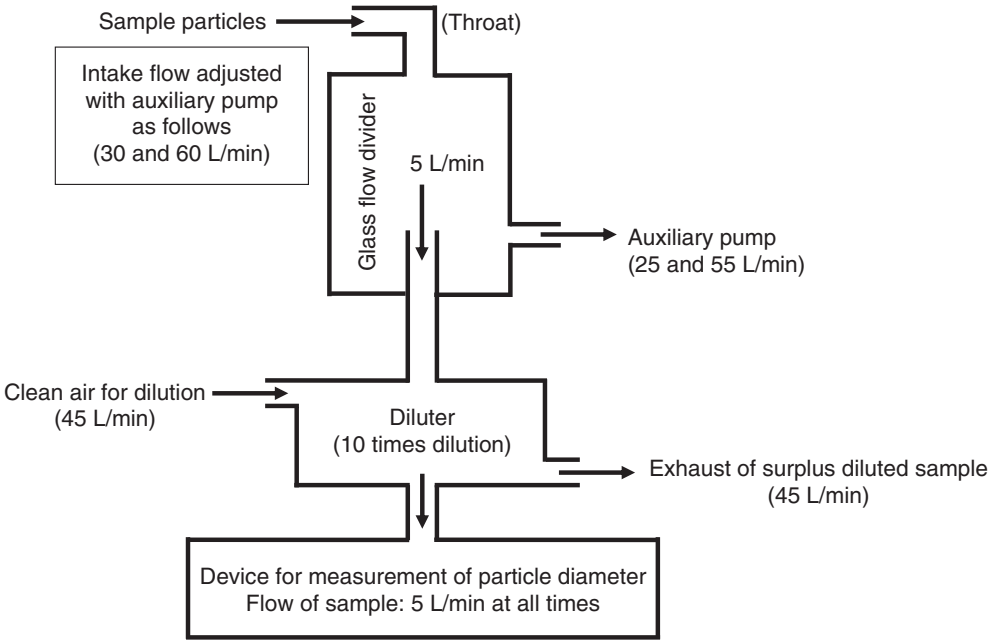

Fig. 1 Flow line for measurement of particle size.

from some devices as well as large differences in the percentage of aerosolization between certain devices for DPI preparations. However, there are very few reports comparing the performance of several devices using the same method.[2,3] As well with the recent introduction in Japan of MF-DPI and BFC-DPI, there is little data available on these new preparations. The present study was undertaken to analyze and compare the performance of the main devices for 5 DPI preparations (FP-DPI, BUD-DPI, MF-DPI, SFC-DPI, and BFC-DPI). The devices tested were Diskus for FP-DPI and SFC-DPI, Turbuhaler for BUD-DPI and BFC-DPI, and Twisthaler for MF-DPI.

METHODS

AEROSOL SAMPLING

Figure 1 shows the flow line for measurements of the particle size of the drug aerosol. In the present study, we used 60 L/min, which is the mean inhalation flow rate for asthmatic patients,[4] and 30 L/min at the suction flow rates, because some patients who have low inspiratory flow cannot inhaled DPI preparations. Because the sample flow rate of the aerodynamic particle sizer (APS) spectrometer Model 3321 (TSI Incorporated, MN, USA) is fixed at 5 L/min, we set the target suction flow rates (30 and 60 L/min) with an auxiliary suction pump combined with a glass flow divider. The apparatus was regularly calibrated using STADEX SC-103 S (JSR Corporation, Tokyo, Japan). All experiments were performed under steady flow through the glass flow divider at each suction flow rate. For all devices, to generate aerosols by wedging the device inlet into the inlet of the glass flow divider, a carbon-mixed silicone tube was attached to the glass flow divider inlet. This tube can be made electroconductive to minimize aerosol particle attachment. Before the start of the measurement, it was confirmed that this electroconductive tube was wedged in a reliable manner into the inlet of each device. Because the maximum concentration compatible with the APS spectrometer was 1,000 particles/mL, the sample concentration was diluted 1 : 10 with a diluter. When actually analyzed, a considerable amount of coarse aggregates of powder hit the throat area of the glass tube, resulting in sedimentation within the flow divider. Thus, the measurement of the particle size of the drug aerosol with the APS spectrometer was only possible for the fine-aerosolized part in the case of DPI preparations.

PARTICLE SIZE MEASUREMENT

Within the APS spectrometer, the particle size of each individual aerosol is measured as an aerodynamic diameter using a time-of-flight principle. A special acuate nozzle with a very small inner diameter is fitted at the inner side of the sample line tip, and sample particles are accelerated during passage through this nozzle. The sample particles accelerated with this nozzle are carried to the detector unit, where they pass through 2 laser beams. The time needed for 1 sample particle to pass through 2 laser beams (time-of-flight) is analyzed every 4 nanoseconds, allowing high temporal resolution. Thus, since this transit time depends on the particle size, the APS spectrometer is designed to conduct a real-time measurement of the distribution of the particle size as

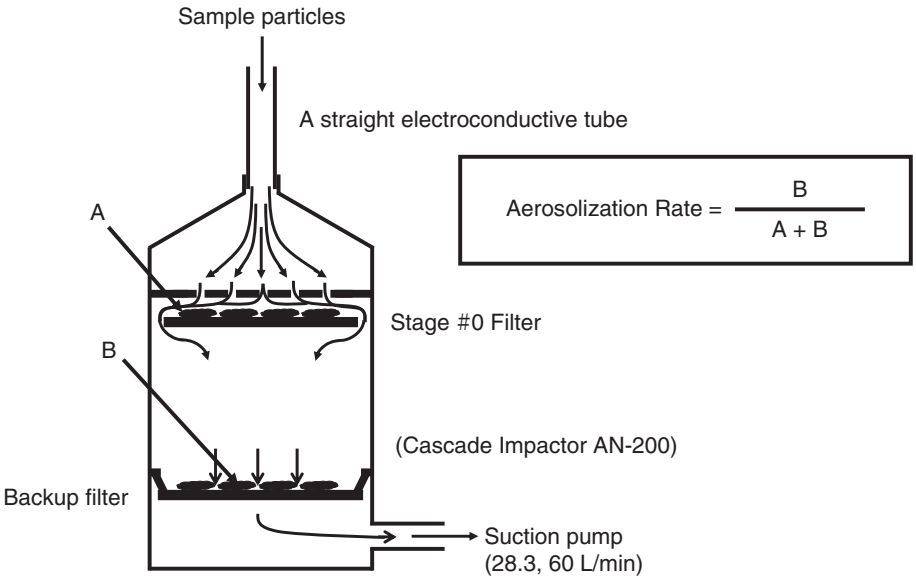

Fig. 2 Flow line for measurement of the percentage of aerosolization.

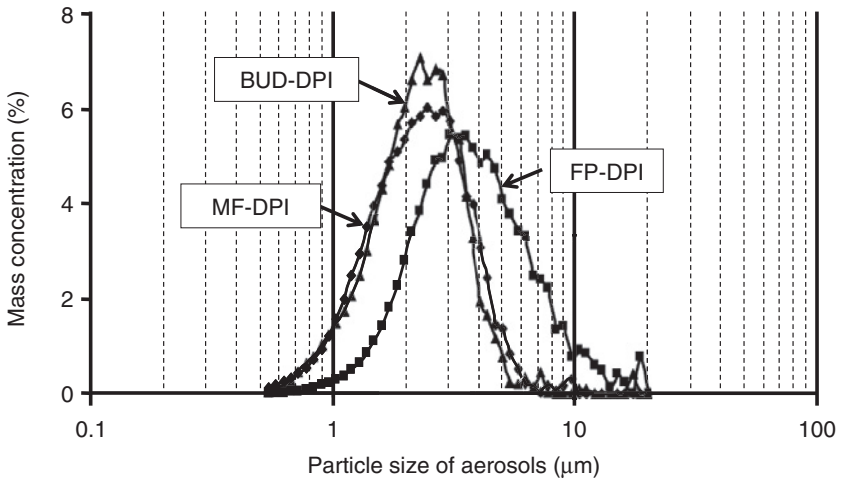

Fig. 3 Distribution of the particle size of aerosols generated from devices for dry powder inhaler of inhaled corticosteroid. The mass concentration for each particle size channel (Y-axis) is shown as a percentage relative to the sum total of the mass concentration for aerosols of each drug (100%) at an inhalation flow rate of 30 L/min.

aerodynamic diameter by measuring the time needed for passage of individual sample particles.

The APS spectrometer Model 3321 is capable of measuring particle sizes between 0.5 and 20 μm in terms of aerodynamic diameter and yields data in units of particle number per mL. Because it is designed to conduct evaluations on the basis of the specific gravity at 1 g/mL of equivalent aerodynamic diameter, the volume is determined with a computer program from the aerodynamic diameter measured with the APS spectrometer, followed by conversion of the specific gravity and particle number into mass. For comparison of the data from a number of drug preparations, the sum total of mass of drug aerosols was deemed as 100%, and the mass of each particle size channel was expressed as percentage relative to the sum total, followed by graphic representation of the frequency distribution and cumulative mass distribution. The coefficient of variation in our measurement of MMAD was 2.84%. Therefore, our method employed for measurement of MMAD is highly reproducible.

MEASUREMENT OF PERCENT AEROSOLIZATION

Since, during the actual measurement of the devices,

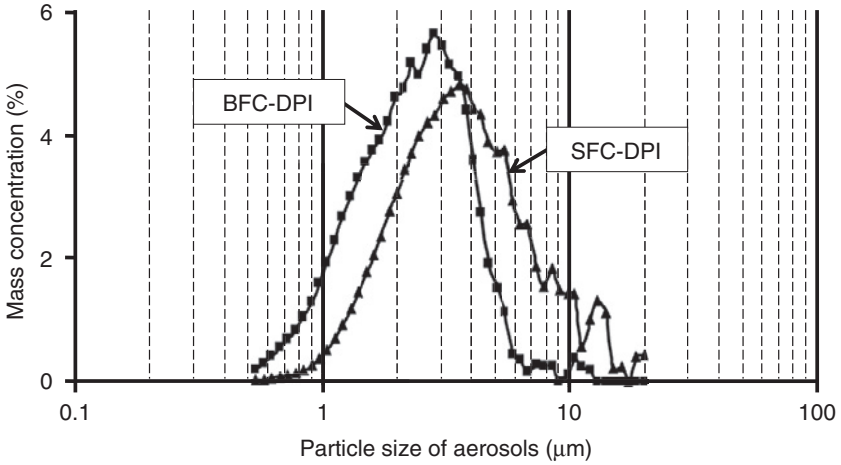

Fig. 4 Distribution of the particle size of aerosols generated from devices for dry powder inhaler of combined drug. The mass concentration for each particle size channel (Y-axis) is the same in Figure 3.

Table 1 Mass median aerodynamic diameter for each preparation of inhaled corticosteroid at suction flow rates of 30 and 60 L/min

Devices	Suction flow rate	
	30 L/min MMAD (μm)	60 L/min MMAD (μm)
FP-DPI (Diskus)	3.63	3.58
BUD-DPI (Turbuhaler)	2.29	2.04
MF-DPI (Twisthaler)	2.31	2.51
SFC-DPI (Diskus)	3.55	3.34
BFC-DPI (Turbuhaler)	2.36	2.20

The values of MMAD for each device at each suction flow rate are averages of the values measured in 6 tests.

Table 2 Percentage of aerosolization of DPI preparations at inhalation flow rates of 28.3 and 60 L/min

Devices	Suction flow rate	
	28.3 L/min (<11 μm)	60 L/min (<7.6 μm)
FP-DPI (Diskus)	6.2%	5.9%
BUD-DPI (Turbuhaler)	47.0%	78.2%
MF-DPI (Twisthaler)	19.8%	43.5%
SFC-DPI (Diskus)	5.7%	7.5%
BFC-DPI (Turbuhaler)	37.5%	86.7%

coarse aggregates of powder were found at the throat and the bottom of the flow divider, the percentage of the drug aerosolized by each device was measured using only stage #0 and backup filters of the Andersen non-viable sampler model AN-200 (Tokyo Dylec Corp, Tokyo, Japan). As shown in Figure 2, the sample was introduced via a 20-cm long straight electroconductive tube with no obstacles such as the flow divider. The collection plate of the stage #0 filter is capable of capturing aerosols over 11 μm in size at a suction flow rate of 28.3 L/min and over 7.6 μm at a suction flow rate of 60 L/min. In view of the possibility that once the particles hit the collection plate of the stage #0 filter they are dispersed again without being captured, we used a stainless steel coated the surface with grease as a capturing collection plate.

RESULTS

AEROSOL PARTICLE SIZE

The particle size distribution of aerosols generated from each device for a mass aerodynamic diameter range of 0.5-20 μm is shown in Figure 3 for ICS preparations and Figure 4 for combined drug preparations at a suction flow rate of 30 L/min. A similar distribution of aerosol particle size is shown for an inhalation flow rate of 60 L/min. As shown in Figure 3, a monomodal distribution less than 5 μm peaking at approximately 2 μm was recorded with the Turbuhaler with BUD-DPI and the Twisthaler with MF-DPI. In contrast, the Diskus with FP-DPI showed a polydisperse distribution, ranging from 0.5 to 20 μm and peaking at approximately 3 μm. As shown in Figure 4, the particle size of aerosols produced by both the Turbuhaler and Diskus devices had almost similar distributions regardless of the type of drug that they contained. The mass median aerodynamic diameter (MMAD) at 2 different suction flow rates are shown in Table 1. With the exception of the Twisthaler for MF-DPI, the Diskus and Turbuhaler tended to have a smaller MMAD as the suction flow rate increased.

PERCENTAGE AEROSOLIZATION

As shown in Table 2, the percentages of DPI preparations converted into aerosols with a particle size less

than 11 μm at a suction flow rate of 28.3 L/min were 5.7-6.2% using the Diskus, 37.5-47.0% using the Turbuhaler, and 19.8% using the Twisthaler. At a suction flow rate of 60 L/min, the conversion of the DPI preparations into aerosols with a particle size less than 7.6 μm were 5.9-7.5% with the Diskus, 78.2-86.7% with the Turbuhaler, and 43.5% with the Twisthaler.

DISCUSSION

Using the APS spectrometer Model 3321,[5,6] we evaluated the performance of the main devices used for DPI, namely Diskus, Turbuhaler, and Twisthaler. Typically, cascade impactors are most frequently used for measuring the MMAD of these devices. Although cascade impactors are relative inexpensive aerodynamic sizing instruments, the precision of cascade impactor measurements is limited due to the fact that the stage collection efficiency curves of impactors are not perfectly sharp[7,8] and because of manufacturing tolerances.[9,10] In addition, the APS spectrometer Model 3321 allows for accurate size distribution measurements to be made in minutes as opposed to the hours required to conduct and analyze size distribution measurements from cascade impactors.[5] As a result, we gained continuous distribution of the particle size of aerosols generated from these devices.

An advantage of DPI preparations is that since the drug supplied in this form is aerosolized only by the patient's own inspiratory power, no extra energy is needed for aerosolization. Accordingly, these preparations are unlikely to cause environmental damage. A shortcoming of DPI preparations, however, is that they cannot be inhaled by some patients who have low inspiratory flow. Therefore, in the present study, we used 60 L/min, which is the mean inhalation flow rate for asthmatic patients,[4] and 30 L/min at the suction flow rates.

As shown in Table 1, even at a suction flow rate of 30 L/min, the MMADs of these devices were between 2.29 and 3.63 μm, which are suitable for movement and deposition in the central airway.[11] As shown in Figures 3 and 4, a mono-modal distribution of aerosol particle size less than 5 μm was recorded with the Turbuhaler and Twisthaler. Therefore, fine aerosol particles of BUD-DPI and MF-DPI may move and deposit from the central airway to the parenchymal lungs. Diskus showed a polydisperse distribution, ranging from 0.5 to 20 μm. Although the sites of lung deposition of the 2.7 and 3.6 μm aerosols of MMAD were similar,[12] aerosols particles more than 6 μm generated from the Diskus may not reach the central airway.

For Diskus, the percentage of the drug converted into aerosols with a particle size of less than 10 μm was calculated to be only 5.7-7.9% of the bulk formulation delivered. This could be because of the high amount of lactose in the formulation. Actually, some reports[13,14] have suggested that FP rather than lactose undergoes aerosolization, however those analysis were based on the Electronic Lung™, which has a large, 11 L space,[15] the "sampling chamber", between the inhalation device and the cascade impactor. In addition, the systemic availability of fluticasone via Diskus has been reported to be about 13%.[16] Therefore, without the Electronic Lung, it is important that the manufacturer should disclose what percent of actual drugs is included in fine aerosol particles less than 5 μm. This information will help to safeguard the patients against local adverse reactions such as hoarseness and oral candidiasis.

For Turbuhaler for BUD-DPI and Twisthaler for MF-DPI, at a suction flow rate of 60 l/min, the percentage of aerosols with a particle size of 0.8-5 μm was calculated to be 73.9% and 40.0%, respectively. Although we could not conclude whether this difference was due to the blend ratio of anhydro-lactose in the agglomerate, these devices are expected to facilitate the delivery and deposition of aerosols in an extensive area of the central and peripheral airways. However, even when the percentage of aerosolization is high, the drug will not exert anti-inflammatory action in the peripheral airways unless the inspired air reaches the airways. It is essential that the patients using these devices inspire deeply after deep expiration, because deep expiration does not block inhalation of agents.[17] In addition, since an increase in the inhalation flow rate elevates the percentage of aerosolization, it is necessary to instruct the patient to inspire forcefully.

In the present study, we have displayed *in vitro* differences in the aerosolization among different devices for DPI of ICS and combined drug preparations. Prescribers of these preparations should consider whether the patients will benefit more from the treatment of the central airways versus the peripheral airways. In addition, attention should also be paid to the performance of the inhalation technique planned for use.

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